Cancer is a term referred to a disease caused by genetic or environmental factors that result in critical-gene mutations the leading cause of mortality worldwide.1 The World Health Organization estimated that the number of cancer-related deaths will increase by 2030.2 Therefore, effective treatment of cancers remains urgently needed. Surgery, radiotherapy, and chemotherapy are the first-line treatment options for most cancers.3 Conventional chemotherapy, a fundamental approach to cancer treatment, distributes drugs through the bloodstream to various organs, where it interferes with DNA synthesis and mitosis in rapidly proliferating cells and causes cell-cycle arrest.4,5 However, chemotherapy is associated with multidrug resistance (MDR), nonspecific drug distribution, and systemic toxicities.6 Chemotherapeutic drugs are non-selective; their cytotoxic effects can damage healthy tissue cells, leading to adverse toxic effects, such as cardiotoxicity in the case of adriamycin7 or hepatotoxicity in the case of camptothecin.8 In addition, conventional chemotherapeutic drugs are less bioaccessible to cancer tissues; therefore, high dosages are required, which in turn produces toxicity in normal cells and increases the likelihood of multi-drug resistance.9 The efficacy of cancer therapy is influenced by drug tolerance, effective drug delivery, and duration of drug action, among others, which considerably restrict its application.10 Consequently, conventional cancer treatments are associated with disadvantages, such as difficulty in achieving treatment, cancer recurrence, and side effects.11 Despite considerable advances in cancer treatment, cancer-related morbidity and mortality rates continue to increase.12 According to statistics, the age-standardized cancer incidence rate is 201.7/100□000 in China, 319.2/100□000 in the United Kingdom, and 352.2/100□000 in the United States. At the same time, the cancer mortality rate is 130.1 per 100□000 in China, 102.6 per 100□000 in the United Kingdom, and 91.0 per 100□000 in the United States.13 Therefore, highly effective and less toxic strategies that can differentiate between cancer and normal cells, selectively target cancer tissue, and respond “intelligently” to the complex microenvironment of the cancer are warranted. studies have demonstrated that the accumulation of some ruthenium complexes in the nucleus is far lower than those in other subeellular regions. Some nonnuclear targets, such as the cell surface, and especially mitochondria, have also been reported to be targets for the anticancer activity of some Ru(u) complexes. Mitochondria play a significant role in cellular meta- bolism and, under certain cellular conditions, release molecules that can activate the extrinsic and intrinsic apoptotic pathways.** Two key characteristics of mitochondria include mitochondrial DNA nucleoids anchored to the matrix side of the inner membrane, and the extremely negative membrane potential (-160 to 180 mV) caused by the proton gradient across the mitochondrial inner membrane. The negative potential of the inner membrane attracts lipophilie cations, including metal complexes such as the Ru(u) complexes. The lipophilicity of Ruju) complexes can be modulated by adjusting the ligands and the valence of complexes, which partly affects the uptake and targeting of Ru(u) complexes. For example, Gasser and co-workers found that [Ru(dppz), (CppH)] (1a. CppH 2-(2-pyridyl) pyrimidine-4-carboxylic acid) possesses two positive charges. and accumulates in the mitochondria (Fig. 4). In addition, la had significant anticancer efficacy in A2780 cancer cells, with an IC value of 2.8 $\mu$M, which was similar to that of cisplatin (IC 2.9 M. Moreover, ta was more efficacious in cisplatin-resistant A2780/CP70 cells than cisplatin and less. cytotoxic than cisplatin in healthy MRC-5 cells." Dickerson and co-workers reported that the Ru(n) complex 1b, carrying an overall charge of +2,

can localize to the mitochondria and induce rapid membrane depolarization and necrotic cell death. In contrast, its analogue Run) complex (1c), carrying an overall